REMME AND SWEDWERG

Remme and Swedwerg, "Guidelines for the diagnosis and treatment of chronic heart failure," Eur Heart J. 2001; 22: 1527-60 ("Remme and Swedwerg," Exhibit B), further undermines the premise of the present rejection that therapies for one class of CHF patient would be used in the treatment of other CHF classes. In particular, Remme and Swedwerg advise that the aldosterone antagonist spironolactone is recommended for more severe heart failure (NYHA class III, IV), but that it is not recommended for mild to moderate heart failure (NYHA class II) because its efficacy for mild to moderate heart failure has not been shown. (Table 18 in page 1545 and Table 21a in page 1551.)

Remme and Swedwerg thus suggests that the efficacy/safety of a medicament for heart failure may be markedly varied depending on the severity of heart failure (NYHA class I-IV). Therefore, contrary to the premise of the present rejection, it is not the case that a compound suitable for the treatment of one class of CHF would have been reasonably expected to be suitable for treatment of another CHF class.

Thus, the present inventors' discovery that tolvaptan is very useful for heart failure (NYHA class IV) could not have been reasonably extrapolated from the characterization of Ogawa and Gheorghiade as providing its potential use as a diuretic in NYHA class I-III CHF. Indeed, compared with the references on which the Office relies, the present application is a first disclosure that the compound of the present invention exhibits a very potent activity for severe heart failure (NYHA class IV) with lower adverse effect.

DIURETICS ARE NOT SUITABLE FOR ALL PATIENTS SUFFERING FROM CHF.

Although, as noted above, it is clear from Remme and Swedwerg that pharmaceutical therapies must be considered separately for each class of CHF, the Office relies on Remme and Swedwerg to support the use of a diuretics used with less severe II CHF patients for patients suffering from more severe NYHA class IV CHF. (Office Action, pg. 3.) However, the use of diuretics is not always useful for a patient suffering from CHF. Indeed, even Remme and Swedwerg, upon which the office relies, notes that excessive preload reduction due to diuretics and ACE inhibits is among the most frequent causes of worsening heart failure. (Remme and Swedwerg, Table 22, pg. 1552.)

Other references likewise indicate that a diuretic may be associated with an increased risk of arrhythmic death. For example, Cooper H. A., Circulation 1999, 100, p 1311-1315 ("Cooper," Exhibit C) concludes that "baseline use of a non-potassium-sparing diuretic was associated with an increased risk of arrhythmic death...." (Cooper, Abstract, pg. 1311 emphasis added.)

SAFETY AND EFFECT OF TOLVAPTAN

In contrast to the warnings and uncertainty in the art, the presently claimed compound has improved the symptom of severe heart failure without the increase of patient mortality. This is disclosed, for example, in Tables 2-7 in the present specification. This result is unexpected, and the Office certainly has not cited any evidence that ordinary diuretics (non-potassium-sparing diuretics) exhibit the therapeutic improvement without such risk. Indeed, the Gheorghiade reference relied upon by the Office certainly does not also disclose such high effect and low risk.

The unexpected long-term safety and effect of the presently claimed compound (tolvaptan) in the treatment of NYHA Class IV CHF has been also confirmed in a recent publication based on the EVEREST Outcome Trial, specifically JAMA, March 28, 2007 Vol. 297, No. 12, P. 1319-1331 ("EVEREST," Exhibit D.) See, for example, the conclusion on page 1319 and the mortality data relative to placebo in Table 2 in page 1323. Accordingly, the present invention is based on the unexpected discovery that the presently claimed compound (tolvaptan) in predefined doses is potently effective and safe medicament for severe heart failure (NYHA class IV) and hence objectively non-obvious.

Thus, even if, as contended by the Office, the presently claimed compound might be useful as a diuretic, the safety in actually treating NYHA Class IV CHF is unexpected and more than sufficient to overcome the rejection.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Conclusion

Applicant respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing the claims in condition for allowance. Applicant submits that the proposed claim amendments do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships were previously claimed. Therefore, this Amendment should allow for immediate action by the Examiner.

Furthermore, the proposed Amendments place the claims in better form for appeal, should the patentability of the pending claims be further disputed by the Office.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916. The Examiner is invited to contact Applicant's undersigned representative by telephone at (202) 408-4092 to address any issues in this application.

Respectfully submitted,

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Dated: November 30, 2007

By: _____

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Attachments:
A) The Heart Failure Society of America Guidelines, Journal of Cardiac Failure 1999; Vol. 5: 357-82.
B) Remme and Swedwerg, Guidelines for the diagnosis and treatment of chronic heart failure, European Heart Journal 2001; 22: 157-60.
C) Cooper H. A., Circulation, Journal of the American Heart Association 1999, 100; 1311-1315.
D) JAMA, March 28, 2007, Vol. 297, No. 12, 1319-1331.

A The Heart Failure Society of America Guidelines, J. Card. Fail. 1999; 5: 357-82.
B Remme and Swedwerg, Guidelines for the diagnosis and treatment of chronic heart failure, Eur Heart J. 2001; 22: 1527-60.
C Cooper H. A., Circulation 1999, 100, p 1311-1315.
D JAMA, March 28, 2007 Vol. 297, No. 12, P. 1319-1331.